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DIAGNOSTIC RELEVANCE AND LABORATORY EVALUATION OF CALCULATED GLOBULIN IN THE DETECTION OF ANTIBODY DEFICIENCY

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SUMMARY
Antibody Deficiency (AD) is a heterogeneous group of immune disorders characterized by decreased serum immunoglobulin levels responsible for recurrent bacterial infections. AD, which can be primary or secondary, represents the most common immune abnormality in adulthood, with high morbidity and mortality due to diagnostic delays estimated at five to six years, partly due to the high cost of specific diagnostic tests, hence the interest in developing rapid and inexpensive screening tests, including Calculated Globulin (CG). Our work reports the results of the use of CG defined by the difference between serum levels of total protein and albumin, reflecting in accordance with serum levels of Immunoglobulins (Ig), and thus presenting a predictive value in the early diagnosis of AD. This is a retrospective study conducted at the laboratory of Sheikh Khalifa International University Hospital from January 2022 to September 2022 including 2456 patients. Analysis of the samples found a GC rate varying between 10 and 100 g/l, in patients with an average age of 55 years and a slight female predominance (52%). Based on the results of a pilot study, as well as the clinical information provided, a CG threshold of 18 g/l allowed the detection of subjects with IgG levels below 7 g/L with high sensitivity and specificity. Thus, this inexpensive and widely available method makes it possible to detect AD patients, and consequently to reduce the diagnostic delay and the time required for management and treatment with replacement immunoglobulin.

KEYWORDS: Antibody Deficiency, Calculated Globulin, Immunoglobulin, IgG.

INTRODUCTION

Antibody deficiency (AD) constitutes a heterogeneous group of immune disorders characterized by reduced serum immunoglobulin levels and a predisposition to recurrent bacterial infections.[1] AD can be primary (PAD) or secondary (SAD) and represents the most common immune abnormality in adulthood.[3]

Indeed, it is an uncommon group of disorders characterized not only by its high prevalence (one in 25,000 to 50,000 people)[1], but also by its high morbidity and mortality associated with the exacerbation of health resources by a delay in diagnosis; estimated at between five and six years reported in the United Kingdom and the United States; before the start of appropriate treatment.[4],[2] The German National Registry of Primary Immunodeficiency suggests that the situation has not improved and may even have worsened.[5]

This is despite efforts by the European Society of Immunodeficiency Diseases (ESID) and others to reduce delays by publishing guidelines on the diagnostic pathway, while proposing clinical strategies to reduce diagnostic delays include improving education and awareness of AD in primary and secondary care, patient-centered screening, and use of the "10 warning signs" of primary immunodeficiency.[4],[6],[7]

Furthermore, the high cost of specific diagnostic tests is considered an important factor in diagnostic delay in our context, which affects the quality of life and the incidence of end-organ damage for these patients.[8],[2] Many of these patients therefore have multiple contacts with health systems during the years between the development of the disease and diagnosis. During this period, it is common to have to perform several biological tests and multiple hospital stays. These episodes provide an opportunity to identify patients with unsuspected immunodeficiency and therefore reduce diagnostic delays. Thus, laboratory approaches have consisted of opportunistically detecting cases of antibody deficiency through rapid and inexpensive routine

screening tests.

It is recognized that patients with hypogammaglobulinemia may have a low Calculated Globulin (CG) fraction, estimated as the difference between serum total protein (TP) and albumin (AL).[9] Indeed, CG is part of the liver function test profile and determines the serum globulin concentration, of which immunoglobulins (Ig) are a major component. So far, the main use of CG is the detection of paraproteins when the level is elevated.[10] Our study investigated the possibility of using low GC levels to detect antibody deficiency.

METHODS

Based on the results of a pilot study determining a threshold of CG < 18 g/l to detect AD subjects with an IgG level < 7 g/L[2], we conducted a retrospective analysis at the laboratory of the Sheikh Khalifa International University Hospital from January 2022 to September 2022.

Anonymous samples were analyzed using the Bromocresol Green (BCG) colorimetric method for albumin and the Architect Biuret method for total protein (TP). Immunoglobulin levels were then measured by nephelometry. Clinical and laboratory data were analyzed using Microsoft Excel.

Was used using percentages and frequencies for qualitative variables represented in the form of graphs as well as mean values and extremes for quantitative variables.

Data collection was carried out taking into consideration global ethical rules relating to respect for confidentiality and the protection of patient-specific data.

RESULTS

During our study period, 2471 requests were processed in the laboratory of the Sheikh Khalifa International University Hospital. The analysis of the samples found a GC rate varying between 10 and 100 g/l, of which only 3% had a CG rate <18 g/L.

A slight female predominance was noted with 52% (Figure.1)

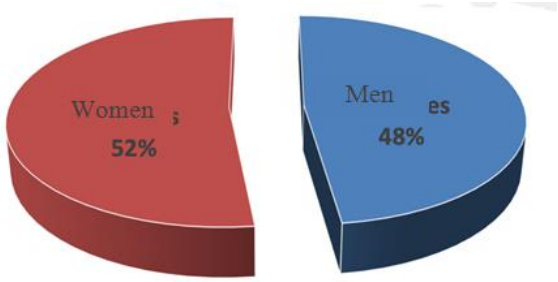

Figure 1: Distribution by gender.

Our study found an average age of 55 years. In addition, the CG rate < 18g/L was most found in patients at extreme ages (Figure 2).

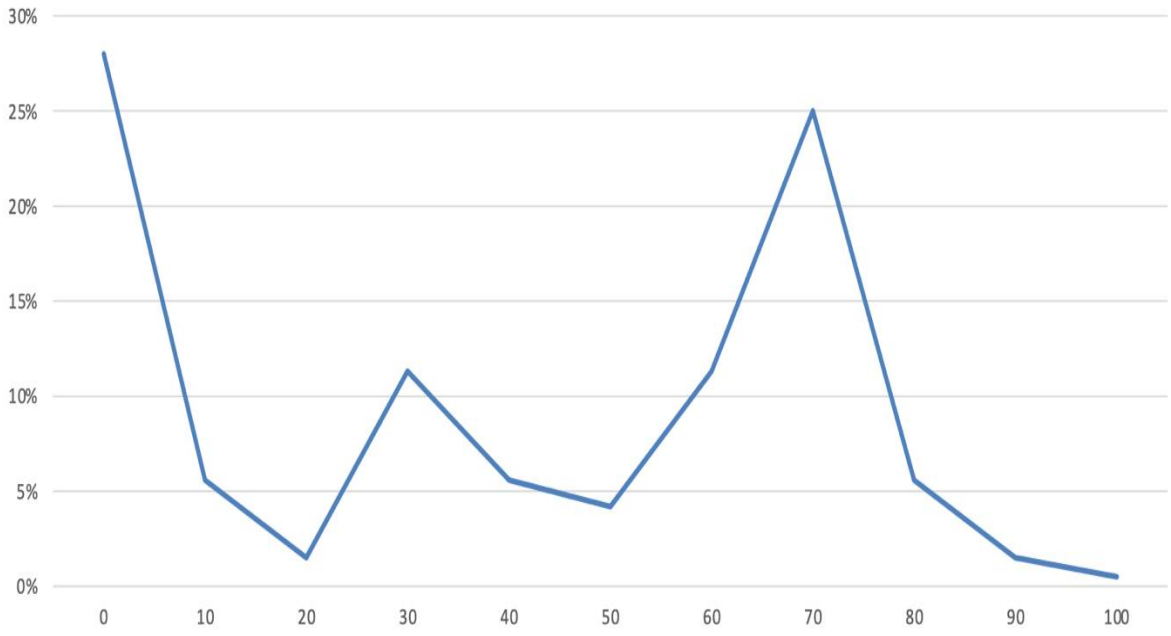

Figure 2: Effect of age on the proportion of patients with CG <18 g/L.

Our cohort showed a linear relationship between IgG and CG values with a wide range of IgG levels for each CG level (Figure 3).

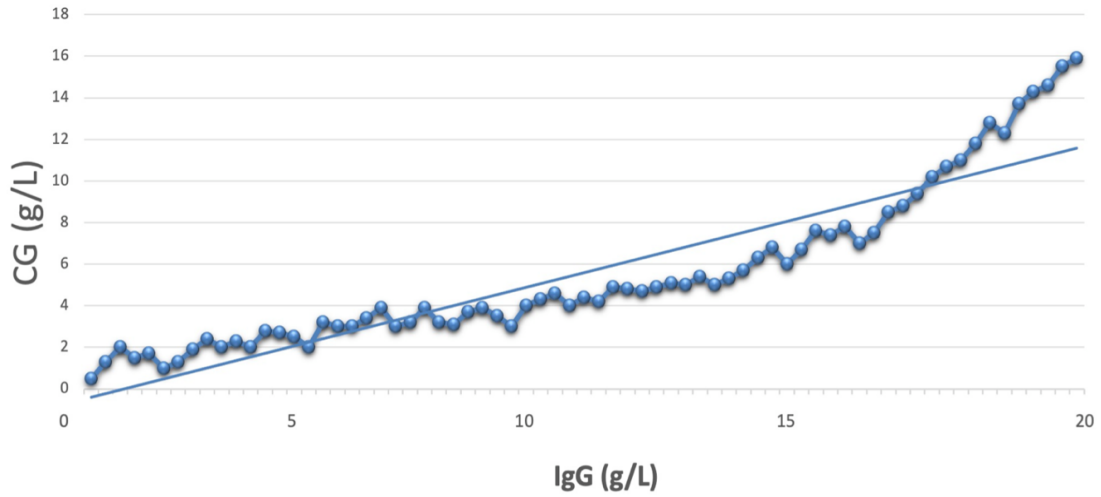

Figure 3: Correlation between CG values and serum IgG levels.

Furthermore, the number of samples at each IgG level is shown for samples with a calculated globulin (CG) of < 18 g/L with only 33% of samples recorded with an IgG level within the normal range (6-16 g/L); 42% of samples had an IgG of < 4 g/L. (Figure 4)

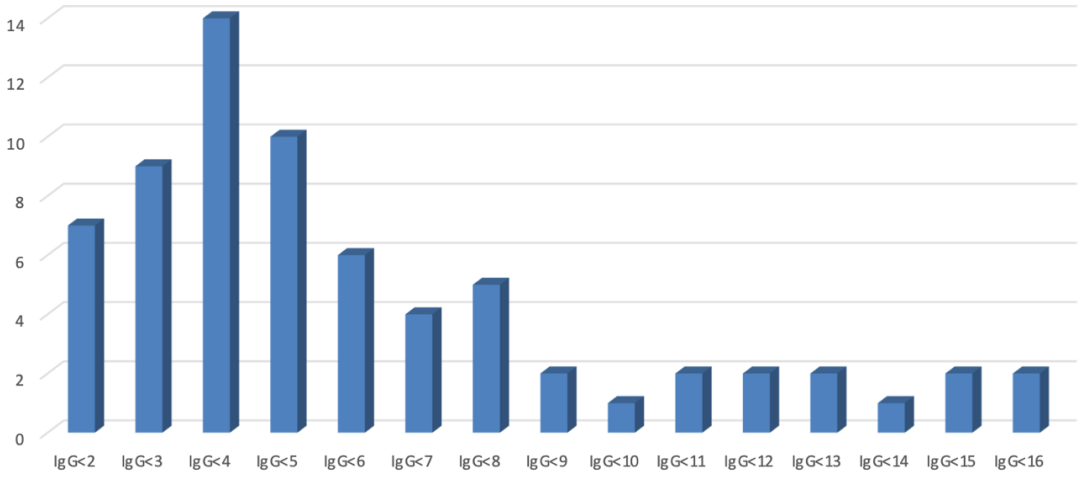

Figure 4: Number of samples at each IgG level.

Although the oncology department was the most involved department with the highest number of samples with low IgG levels, a wide range of clinical specialties and primary care were represented in our analysis (Figure 5).

Clinical details of samples with IgG levels < 4 g/L demonstrated AD in 7% of known SAD patients, followed by 5% for immunosuppressive treatment and known diagnosis of Lymphoma.

DISCUSSION

CG represents the difference between total protein and albumin results in the liver function profile. CG is simple, inexpensive, and widely available. Indeed, as total protein and albumin are currently routinely performed as part of the liver profile, no additional testing costs are incurred. CG also meets other criteria required for a screening test: it is acceptable to the population, and there is effective treatment for patients identified through early detection, leading to improved long-term prognosis.[2],[11]

Early diagnosis and effective treatment are crucial to reduce the incidence of irreversible chronic complications related to AD that affect the long-term prognosis and quality of life of patients.[13] Indeed, several studies have demonstrated that diagnostic delay is associated with reduced patient survival[14], and also affects the costs of managing these patients, and more generally Primary Immune Deficiency (PID). In a study on the economic impact of PID conducted by the Jeffrey Modell Foundation[15], the implementation of immunoglobulin replacement therapy resulted in an

annual saving per patient of $78,166 despite immunoglobulin costs. In addition, the introduction of CG screening could improve the early detection of patients with SAD.

According to A. Pecoraro et al, a CG cutoff of 19 g/l was determined to detect patients with IgG levels above 600 mg/dl with a sensitivity of 70% and a specificity of 75%.[1] These results are consistent with the results of the CG study by Jolles et al., where a cutoff of 18 g/l, with a sensitivity of 66% and a specificity of 78% for samples with IgG < 500 mg/dl, was used in the prospective analysis.[12]

There are potential limitations to this screening approach. Primarily, the sensitivity and specificity values of GC are potentially limited by the fact that IgG represents only about 30% of the total serum globulin fraction, which also includes the acute-phase proteins alpha and beta globulins. Therefore, acute inflammation, occurring in patients with antibody deficiency, may cause an increase in alpha and beta globulins and could potentially mask low gamma globulin levels. Furthermore, this screening approach has not been established for children, whose normal IgG values vary with age. Potential limitations in the specificity of this test could lead to unnecessary immunoglobulin testing in non- hypogammaglobulinemic patients.

CONCLUSION

In conclusion, the results of this study confirm the relationship between IgG concentrations and GC fraction. Furthermore, they demonstrate the potential utility of a GC-based screening test as a tool to reduce diagnostic delays, improve long-term prognosis, and reduce AD-related healthcare costs, particularly for patients with unsuspected primary or secondary hypogammaglobulinemia. Further studies appear necessary to validate the role of this screening in a larger cohort of patients.

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